

## Influence of glyceryl trinitrate and nifedipine on coronary sinus blood flow and global myocardial metabolism during coronary artery operation

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**SUMMARY** The effects of intravenous infusions of glyceryl trinitrate and nifedipine on systemic haemodynamic function, coronary haemodynamic function, and global myocardial metabolism were compared in two groups of eleven patients with unimpaired left ventricular function undergoing elective coronary artery operation who were anaesthetised with high dose fentanyl. Severe post-sternotomy hypertension developed in three patients in the glyceryl trinitrate group who were resistant to the hypotensive effect of this agent. All patients given nifedipine remained haemodynamically stable. Coronary sinus blood flow and myocardial oxygen consumption increased and coronary vascular resistance decreased after sternotomy in the nifedipine group but not in the glyceryl trinitrate group. There is no satisfactory explanation for the apparently paradoxical increase in myocardial oxygen consumption in the patients given nifedipine. This phenomenon did not appear to be associated with any detrimental effect of left ventricular function.

Thus nifedipine was better than glyceryl trinitrate for the control of post-sternotomy hypertension in patients with good left ventricular function. Intravenous nifedipine is not recommended, however, for the intraoperative control of blood pressure in patients with unstable angina or impaired left ventricular function.

Glyceryl trinitrate is often used to control the development of hypertension after sternotomy in patients undergoing coronary artery operation.<sup>1</sup> It reduces blood pressure by both arterial and venous dilatation, with the latter effect usually predominating. This reduction in left ventricular preload and afterload is accompanied by a decrease in myocardial oxygen consumption ( $MVO_2$ ) without significant changes in coronary sinus blood flow.<sup>2</sup>

Recently the calcium channel blocking agent nife-

dipine has been successfully used for the treatment and prevention of hypertensive episodes in patients undergoing coronary artery operation.<sup>3,4</sup> Because of its strong peripheral and coronary artery vasodilating action nifedipine reduces left ventricular afterload and increases coronary sinus blood flow, although  $MVO_2$  does not appear to be significantly decreased.<sup>5</sup>  $MVO_2$  is, however, reduced by nifedipine in the presence of  $\beta$ adrenergic blockade.<sup>6</sup> Most patients presenting for coronary artery operation have been taking  $\beta$  blockers before operation. No information is available on the effect of nifedipine on the coronary circulation and  $MVO_2$  during coronary artery operation.

The present study was designed to compare the effect of glyceryl trinitrate and nifedipine on global myocardial metabolism and coronary sinus blood flow in patients undergoing coronary artery operation.

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## Patients and methods

Twenty two patients scheduled for elective coronary artery operation gave their informed consent to participate in this study, which had the approval of the local medical ethical committee. Patients with left ventricular end diastolic pressure  $\geq 15$  mm Hg, ejection fraction  $\leq 50\%$ , atrioventricular conduction defects, or unstable angina pectoris were excluded from the study. Those undergoing additional operation (for example valve replacement or aneurysmectomy) were also excluded. All patients were taking  $\beta$ adrenergic blocking drugs before operation. Except for nitrates, oral medication was discontinued the evening before operation. Patients were randomly allocated to one of two groups. One group of 11 patients received glyceryl trinitrate at an initial rate of  $3 \mu\text{g/kg/min}$  and another group of 11 patients received nifedipine at an initial rate of  $0.7 \mu\text{g/kg/min}$ . All infusions were given via a syringe pump through polypropylene syringes and infusion lines. Black syringes and lines were used for nifedipine because it undergoes rapid decomposition in light.

Patients were premedicated with oral lorazepam (4–5 mg) two hours before operation. In the operating room two peripheral infusions and an 18 gauge radial artery cannula were inserted under local analgesia. A triple lumen thermodilution pulmonary artery catheter and a Wilton Webster coronary sinus catheter (type CCS-7U 90B) were introduced via the left subclavian vein. The Wilton Webster catheter was advanced into the coronary sinus so that the external thermistor lay 1–1.5 cm from the ostium. We used image intensification fluoroscopy and injection of contrast medium for guidance.

Pancuronium bromide (2 mg) was given after pre-oxygenation, then fentanyl ( $100 \mu\text{g/kg}$ ) was injected over 3 min. When the patient became unresponsive to commands additional pancuronium bromide (6 mg) was given and ventilation was assisted and then controlled manually. After intubation of the trachea, the lungs were ventilated with 50% oxygen in air. Ventilation was adjusted to maintain end tidal carbon dioxide concentration between 4% and 4.5%.

Control measurements were obtained 10 min after intubation and then vasodilator infusion was started. Infusion rates were adjusted to maintain systolic blood pressure at  $\leq 120\%$  of preinfusion values (control) or mean blood pressure  $\leq 100$  mm Hg or both. Infusions were continued as required until the start of cardiopulmonary bypass. Further measurements were obtained 10 min after the start of vasodilator infusion (before operation) and after sternotomy when the pericardium was opened. At

each measuring period a complete haemodynamic profile and thermodilution curves for coronary sinus blood flow were obtained. Blood samples were taken simultaneously from the radial artery and coronary sinus for determination of oxygen tension and saturation, haemoglobin, and plasma lactate concentration. Cardiac output was measured by thermodilution by means of 5 ml boluses of saline at  $0^\circ\text{C}$ . Coronary sinus blood flow was measured by the continuous thermodilution technique.<sup>7</sup> Oxygen saturation ( $\text{SO}_2$ ) was measured by an OSM-II and  $\text{PO}_2$  by an ABL-III (Radiometer, Copenhagen). Lactate concentration was measured by standard enzymatic techniques. Myocardial metabolic indices were calculated according to the following formulas:

$$\text{Oxygen content (CO}_2\text{)} = \text{SO}_2 \times \text{Hb} \times 2.23 + 0.003 \times \text{PO}_2 \text{ (ml/dl)} \quad (1)$$

where Hb is haemoglobin in mmol/l.

$$\text{MVO}_2 = \text{Coronary sinus blood flow} \times (\text{C}_{\text{artO}_2} - \text{C}_{\text{csO}_2}) \text{ (ml/min)} \quad (2)$$

where  $\text{C}_{\text{artO}_2}$  is the arterial content of oxygen and  $\text{C}_{\text{csO}_2}$  is the oxygen content in the coronary sinus.

$$\text{Myocardial lactate extraction} = \frac{\text{Arterial lactate} - \text{Coronary sinus lactate}}{\text{Arterial lactate}} \times 100 \text{ (\%)} \quad (3)$$

$$\text{Coronary vascular resistance} = \frac{\text{Mean blood pressure} - \text{Right atrial pressure}}{\text{Coronary sinus blood flow}} \text{ (mm Hg/ml/min)} \quad (4)$$

## STATISTICAL ANALYSIS

Data were analysed by two way analyses of variance for repeated measurements. Where indicated a modified *t* test was used to identify significant differences between and within groups and *p* values were calculated according to the method of Bonferroni.<sup>8</sup> A value of  $< 0.05$  was considered to be significant. Results are reported as mean (SEM).

## Results

Table 1 shows details of the patients. The two groups were comparable with respect to age, weight, and degree of coronary artery disease. Table 2 shows details of infusion rates and total dose requirements of glyceryl trinitrate and nifedipine.

## HAEMODYNAMIC FUNCTION

Table 3 shows measured and calculated haemodynamic variables for the three measuring periods.

Control haemodynamic variables were not significantly different in the two groups. In the

Table 1 Data on the patients

Group	Age (yr)	Weight (kg)	Number of patients with disease of		
			1 vessel	2 vessels	3 vessels
Glyceryl trinitrate	57.5 (2.1)	75.1 (2.4)	1	4	6
Nifedipine	63.3 (1.7)	75.5 (2.6)	2	1	8

1 kg = 2.2 lb.

group given glyceryl trinitrate, systolic, diastolic, and mean arterial blood pressures were significantly lower ( $p < 0.05$ ) than control values after 10 min of glyceryl trinitrate infusion. There were no significant changes in these variables in the nifedipine group at this time. After sternotomy, although blood pressure was not significantly different from control values in either group, the average mean blood pressure in the glyceryl trinitrate group 2 was higher than the maximum striven for in the protocol. In three patients (27%) in this group hypertension that was resistant to glyceryl trinitrate developed after sternotomy, despite a temporary increase in the infusion rate to a maximum of 25 mg/min.

In the nifedipine group arterial blood pressure was well controlled in all patients until the start of cardiopulmonary bypass. In both groups the mean heart rate after sternotomy was approximately 25% higher than in the control period, although the differences were not statistically significant. Stroke index decreased significantly ( $p < 0.05$ ) in the glyceryl trinitrate group after sternotomy. Systemic vascular resistance after sternotomy was significantly lower ( $p < 0.05$ ) in the nifedipine group than in the glyceryl trinitrate group. Compared with control values, there were no significant changes within or between the two groups for right atrial pressure, pulmonary arterial pressure, pulmonary capillary wedge pressure, cardiac index, left ventricular stroke work index, right ventricular stroke work index, rate pressure product, or pulmonary vascular resistance in the period before cardiopulmonary bypass. There were no significant differences in the number of patients requiring inotropic support or pacing or both after cardiopulmonary bypass.

#### CORONARY HAEMODYNAMIC FUNCTION AND MYOCARDIAL METABOLISM

Table 4 shows coronary sinus blood flow and myocardial metabolic variables. Control values of  $MVO_2$ , coronary sinus blood flow, coronary vascular resistance, and myocardial lactate extraction were within the normal range in both groups. After the first 10 min of vasodilator administration neither coronary sinus blood flow nor  $MVO_2$  were different from control values. After sternotomy, coronary sinus blood flow and  $MVO_2$  did not change significantly in the glyceryl trinitrate group. In the nifedipine group there was a highly significant ( $p < 0.001$ ) increase in coronary sinus blood flow after sternotomy with a corresponding decrease ( $p < 0.05$ ) in coronary vascular resistance.  $MVO_2$  did not change significantly in the glyceryl trinitrate group after sternotomy. In the nifedipine group there was a highly significant ( $p < 0.001$ ) increase in  $MVO_2$  after sternotomy.  $MVO_2$  and coronary sinus blood flow were also significantly higher ( $p < 0.01$ ) after sternotomy in the nifedipine group than in the glyceryl trinitrate group. There were no significant changes in arterial or coronary sinus oxygen content, oxygen extraction, or lactate extraction at any time in either group. In one patient in each group lactate extraction changed to production after sternotomy.

#### Discussion

Hypertension after sternotomy is common in patients undergoing coronary artery operation.<sup>9</sup> If untreated, the increased ventricular workload and oxygen demand may contribute to perioperative myocardial infarction.<sup>10</sup> The aetiology of this hypertensive reaction is unknown. It does not

Table 2 Mean (SEM) infusion rates and duration of infusion

Group	Infusion rate ( $\mu\text{g/kg/min}$ )			Duration of infusion (min)	
	Drug + 10 min	Post-sternotomy	Total	Post-sternotomy	Total
Glyceryl trinitrate	5.61 (0.66)	9.05 (1.27)	5.89 (0.69)	10.0 (1.3)	33.7 (1.8)
Nifedipine	1.02 (0.20)	1.68 (0.25)	1.06 (0.14)	8.4 (1.4)	32.7 (2.9)

Table 3 Haemodynamic changes (mean (SEM)) in two groups of eleven patients receiving either glyceryl trinitrate (group 1) or nifedipine (group 2)

Variable	Group	Control	Drug + 10 min	Post-sternotomy
SBP (mm Hg)	1	153.4 (7.67)	127.4 (5.83)*	159.6 (9.35)
	2	132.3 (7.64)	118.4 (3.75)	128.2 (5.18)
MBP (mm Hg)	1	105.2 (4.76)	87.9 (3.72)	111.4 (5.63)
	2	93.4 (5.39)	82.8 (2.64)*	90.9 (3.10)
HR (beats/min)	1	70.6 (6.42)	74.1 (7.66)	87.6 (5.75)
	2	66.4 (4.53)	62.7 (4.13)	82.7 (6.26)
PAP (mm Hg)	1	18.1 (1.37)	15.8 (1.53)	17.0 (1.78)
	2	14.7 (1.02)	15.7 (1.28)	20.7 (2.30)
RAP (mm Hg)	1	6.4 (1.01)	5.6 (1.00)	6.5 (0.95)
	2	4.7 (0.79)	5.2 (0.89)	6 (0.95)
PCWP (mm Hg)	1	10.9 (1.11)	8.5 (1.08)	10.1 (1.44)
	2	6.8 (0.68)	8.1 (0.95)	11.5 (1.96)
CI (l/min/m <sup>2</sup> )	1	3.4 (0.33)	3.1 (0.28)	2.9 (0.30)
	2	3.2 (0.35)	2.8 (0.22)	3.4 (0.30)
RPP	1	11029 (1356)	9417 (1161)	13924 (1150)
	2	8892 (1031)	7494 (639)	10623 (1066)
SVR (dyn s cm <sup>-5</sup> )	1	1330 (107)	1244 (132)	1704 (208)†
	2	1261 (101)	1222 (92)	1113 (74)†
PVR (dyn s cm <sup>-5</sup> )	1	94.2 (9.7)	103.8 (11.6)	114.9 (19.1)
	2	113.9 (14.0)	98.8 (14.4)	115.8 (19.0)
LVS WI (g m/m <sup>2</sup> /beat)	1	62.1 (6.2)	50.7 (10.1)	47.2 (5.7)
	2	57.3 (6.3)	46.1 (2.7)	44.1 (5.3)
RVS WI (g m/m <sup>2</sup> /beat)	1	8.0 (1.3)	7.0 (1.8)	4.1 (0.4)
	2	6.6 (0.7)	6.9 (0.6)	8.3 (0.8)
SI (ml/m <sup>2</sup> )	1	48.5 (3.68)	45.8 (7.03)	34.2 (3.62)*
	2	47.7 (3.40)	45.2 (1.96)	40.5 (3.67)

\* $p < 0.05$  compared with control values. † $p < 0.05$  for nifedipine vs glyceryl trinitrate.

SBP, systolic blood pressure; MBP, mean blood pressure; HR, heart rate; PAP, pulmonary artery pressure; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; RPP, rate pressure product; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; LVS WI, left ventricular stroke work index; RVS WI, right ventricular stroke work index; SI, stroke index.

appear to be associated with an increase in plasma catecholamine concentration or to be the result of inadequate anaesthesia.<sup>9</sup>

In patients with coronary artery disease, glyceryl trinitrate dilates both the normal and stenotic areas of the coronary tree<sup>11</sup> and increases regional myocardial blood flow to subendocardial ischaemic areas by increasing collateral flow,<sup>12,13</sup> although total myocardial blood flow may not change.<sup>2</sup> Glyceryl trinitrate rather than nitroprusside is being increasingly used to treat hypertension and to

reduce myocardial ischaemia during coronary artery bypass operation. Although nitroprusside is more effective than glyceryl trinitrate in controlling blood pressure it may contribute to subendocardial ischaemia by reducing collateral flow to ischaemic areas as a result of coronary steal.<sup>14,15</sup> Some patients are resistant to the hypotensive effects of glyceryl trinitrate. Glyceryl trinitrate was ineffective in 30% of patients requiring controlled hypotension during intracranial aneurysmectomy.<sup>16</sup> It also failed to prevent intraoperative myocardial ischaemia in patients

Table 4 Coronary haemodynamic function and myocardial metabolic findings (mean (SEM)) in group 1 (glyceryl trinitrate) and group 2 (nifedipine)

	Group	Control	Drug + 10 min	Post-sternotomy
CSBF (ml/min)	1	94.8 (5.4)	82.7 (2.7)	139.5 (22.3)†
	2	115.5 (10.2)	98.2 (8.4)	192.7 (20.9)*†
CVR (mm Hg/ml/min)	1	1.11 (0.12)	1.01 (0.82)	0.88 (0.13)†
	2	0.89 (0.08)	0.83 (0.08)	0.50 (0.04)††
MVO <sub>2</sub> (ml/min)	1	11.8 (0.7)	9.8 (0.6)	16.5 (2.9)
	2	13.9 (1.3)	11.6 (1.0)	23.9 (2.5)*
MLE (%)	1	46.9 (5.0)	43.1 (6.5)	30.2 (6.0)
	2	38.2 (4.8)	41.0 (4.7)	34.6 (6.8)
O <sub>2</sub> extraction (%)	1	64.7 (5.2)	64.8 (6.8)	63.2 (6.0)
	2	68.7 (1.21)	67.9 (2.4)	69.2 (1.9)

\* $p < 0.001$  and † $p < 0.05$  compared with control values. ‡ $p < 0.01$  for nifedipine vs glyceryl trinitrate.

CSBF, coronary sinus blood flow; CVR, coronary vascular resistance; MVO<sub>2</sub>, myocardial oxygen consumption; MLE, myocardial lactate extraction ratio.

anaesthetised with fentanyl for coronary artery operation.<sup>17</sup>

In the present study three patients in group 1 also failed to respond to glyceryl trinitrate after sternotomy. In these patients it proved impossible to control post-sternotomy hypertension despite very high doses (up to 25 mg/min). Blood pressure could only be controlled by the administration of  $\beta$  adrenergic blocking drugs (practolol 2 intravenous doses of 5 mg) and the addition of isoflurane to the air and oxygen gas mixture.

The calcium antagonist nifedipine is a potent vasodilator of peripheral and coronary arteries. It reduces myocardial oxygen demand by decreasing left ventricular afterload.<sup>18</sup> In conscious patients intravenous nifedipine given during cardiac catheterisation produced transient increases in coronary sinus blood flow without significant reduction of  $MVO_2$ .<sup>5</sup> When propranolol was given before nifedipine, however, there was a significant and sustained reduction of  $MVO_2$ .<sup>6</sup> Intracoronary administration of nifedipine before percutaneous transluminal coronary angioplasty reduced myocardial lactate production during angioplasty.<sup>19</sup> In our study the patients given nifedipine remained haemodynamically stable. In view of the known vasodilating action of nifedipine on the coronary arteries it was not surprising to find an increase in coronary sinus blood flow and a corresponding decrease in coronary vascular resistance. The pronounced increase in  $MVO_2$  in this group was unexpected, however, since there were no significant changes in left or right ventricular workload. The 25% increases in heart rate (found in both groups) can only be at the most a partial explanation for the observed increase in  $MVO_2$ . In four patients given nifedipine, heart rate changed by < 10% after sternotomy, yet coronary sinus blood flow and  $MVO_2$  increased by 56% and 52% respectively.

There is evidence from animal studies that calcium channel blocking agents interfere with catecholamine release and storage in nerve cells and myocardium.<sup>20</sup> Myocardial release of noradrenaline after oral administration of both verapamil and nifedipine has been reported in man.<sup>21,22</sup> An effect on  $MVO_2$  was not reported in these studies. Because we did not measure catecholamines we do not know whether myocardial catecholamine release played a role in the apparently paradoxical increase in  $MVO_2$  in our patients. At the moment we have no satisfactory explanation for the increase in  $MVO_2$  found in this study, which clinically did not appear to be accompanied by any detrimental effect on myocardial function. The patients in our study all had stable angina pectoris and unimpaired left ventricular function before operation. In this group of

patients nifedipine proved to be more effective than glyceryl trinitrate for the control of intraoperative blood pressure. Because of the potentially cardio-depressant effect of nifedipine, however, we cannot recommend its use in patients with impaired myocardial function. Our finding that nifedipine significantly increased myocardial oxygen consumption suggests that caution needs to be exercised in the use of this agent in patients with unstable angina pectoris undergoing coronary artery operation. An additional disadvantage is that compared with glyceryl trinitrate and nitroprusside, which are rapidly metabolised, nifedipine has a relatively long duration of action and thus its effect cannot readily be reversed.

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